NON-PEPTIDE CRF RECEPTOR ANTAGONISTS. David W. Schulz, Robert S. Mansbach, John P. Braselton, Judith L. Collins, Diane Costello, Michael Corman, Audrey Dunaiskis, W. Stephen Faraci, Anne W. Schmidt, Tom Seeger, Jeffrey Sprouse, F. David Tingley III, Elizabeth N. Winston, Yuhpyng L. Chen, James Heym. PFIZER CENTRAL RESEARCH, Groton, CT.

In addition to activating the hypothalamic-pituitary-adrenal (HPA) axis, corticotrophin releasing factor (CRF) is thought to play a role in mediating CNS responses to stress. Various clinical findings suggest that CRF is hypersecreted in certain pathological states, including depression, bulimia, and PTSD. While a CRF antagonist may be useful in treating these and other psychiatric disorders, it is likely that peptides such as alpha helical oCRF(9-41) will have limited utility due to limitations in bioavailability and pharmacokinetics. Therefore, we have sought to identify a nonpeptide CRF receptor antagonist for potential use as a therapeutic agent. Here we describe the properties of CP-154,526, a potent and selective CRF antagonist that exhibits anxiolytic-like properties in animals.

High speed screening of compound libraries using a ^{125}I-oCRF binding assay yielded a low affinity lead (800 nM) that served as a starting point for chemical modifications. These efforts resulted in a series of novel pyrrolo[2,3-d]pyrimidines exemplified by CP-154,526 (butyl-[2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine). CP-154,526 binds with high affinity to CRF receptors (K_i < 10 nM), and fully blocks CRF-stimulated adenylate cyclase activity in rat brain and pituitary. The affinity of CP-154,526 is > 1 microM for all other receptors examined, and it does not affect activation of adenylate cyclase by H_1 or beta agonists. Pretreatment with CP-154,526 antagonizes the increase in plasma ACTH levels in rats caused by CRF, with an ID_{50} of 14 mg/kg s.c. In addition, CP-154,526 blocks centrally-mediated effects of CRF, attenuating the excitation of locus coeruleus neurons evoked by i.c.v. administration of 3 μg CRF (ID_{50} = 2 mg/kg i.v.). In an acoustic startle procedure, CP-154,526 mimics the peptide antagonist D-Phe CRF(12-41) by completely reversing the enhancement in startle amplitude caused by 1 μg CRF i.c.v. Finally, CP-154,526 demonstrates potential anxiolytic activity in a model of "fear-potentiated" startle. Results with alpha helical oCRF(9-41) suggest that the enhanced startle response in this paradigm is mediated by endogenous CRF.

In conclusion, CP-154,526 is the first potent and selective nonpeptide antagonist of CRF receptors. Following systemic admistration, this novel compound blocks CRF receptor mediated effects in the brain. Agents such as CP-154,526 may ultimately have therapeutic utility in treating diseases where excessive stimulation of CRF receptors contributes to pathology.